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(54) Title: TOPICAL COMPOSITIONS CONTAINING THIAZOLIUM COMPOUNDS AND METHODS OF USING SAME

(57) Abstract: It has been surprisingly discovered that thiazolium compounds may be used to topically treat telangiectasia or spider veins. It is believed that the thiazolium compounds act to restore the elasticity, and the healthy size and shape, of the affected arterioles. Accordingly, there is provided a topical composition having thiazolium compounds for skin care, dermatological applications, and the treatment of spider veins. In addition, this invention provides a method of treating spider veins by topically applying a composition having thiazolium compounds.

TOPICAL COMPOSITIONS CONTAINING THIAZOLIUM COMPOUNDS AND METHODS OF USING SAME

Background of the Invention

1. Field of the Invention

The present invention relates to cosmetic and dermatological compositions. More particularly, the present invention relates to cosmetic and dermatological compositions containing thiazolium compounds.

2. Description of the Prior Art

Telangiectasia is a condition characterized by the dilation of one or more superficial arterioles in the human body, such that the effected arterioles become visible through the skin. In some cases, telangiectasia is symptomatic of a more serious disorder. However, telangiectasia occurs in approximately 15% of the population as a purely cosmetic problem. Telangiectasia is aesthetically objectionable and often becomes an increasingly common occurrence as an affected person ages. The objectionable nature of telangiectasia is evidenced by the common name for the disorder, i.e., "spider veins."

Spider veins are readily recognizable because of the characteristic shape and angry, red color of the dilated arterioles. In addition, spider veins typically blanch if pressure is applied to the nearby skin.

There are several techniques presently used to treat spider veins. First, several techniques for the treatment of spider veins involve invasive procedures that are intended to disrupt or destroy the arteriole. For example, hypertonic saline or octadocanol may be injected into a larger artery adjacent to the affected arterioles, which scleroses the larger artery and effective "dries up" the spider veins. However, such invasive techniques are clearly undesirable because they require delicate operations that must be performed under the supervision of a physician.

Alternative techniques use laser light focused on the affected arterioles. Furthermore, pigmented creams can be used to mask the spider veins.

More recently, topically applied compositions have been introduced to treat spider veins. For example, U.S. Patent No. 5,268,176 discloses the use of inositol phosphoric acid and its derivative in the treatment of spider veins. Topical compositions are intended to treat the affected arterioles and have several advantages, such as being non-invasive, simple, and readily available. However, topical compositions are often less than totally effective.

In light of the foregoing, there is an on-going need for a topically applied compositions useful for treating dermatological conditions and, especially, spider veins.

Summary of the Invention

It is an object of the present invention to provide a topical or dermatological composition.

It is also an object of the present invention to provide a topical or dermatological composition useful for the treatment of telangiectasia or spider veins.

It is a further object of the present invention to provide such a composition useful for the treatment of telangiectasia or spider veins, which contains thiazolium, oxazolim, or imidozolium compounds.

It is yet another object of the present invention to provide a method of treating telangiectasia or spider veins.

It has been surprisingly discovered that thiazolium, oxazolium, and imidozolium compounds may be used to topically treat telangiectasia or spider veins. It is believed that thiazolium, oxazolium, and imidozolium

compounds act to restore the elasticity, and the healthy size and shape, of the affected arterioles.

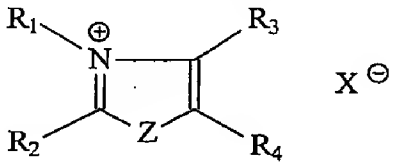
Accordingly, there is provided a topical composition having thiazolium, oxazolium, or imidozolium compounds for skin care, dermatological applications, and the treatment of spider veins. In addition, the present invention provides a method of treating spider veins by topically applying a composition having thiazolium, oxazolium, or imidozolium compounds.

Detailed Description of the Invention

As used herein, "alkyl" means a straight, branched, or cyclic hydrocarbon chain, saturated or unsaturated, and unsubstituted or substituted. "Aryl" means a moiety having an unsubstituted or substituted aromatic ring. "Cyclic" means a moiety having an unsubstituted or substituted non-aromatic ring. "Anion" and "anionic" are interchangeable and refer to any ion or compound having a negative charge.

In accordance with the present invention, compositions and methods have been developed that are believed to treat superficial arterioles affected by telangiectasia. Specifically, it has been surprisingly discovered that the active compounds described herein may be used to topically treat spider veins. It is believed that the active compounds restore the elasticity, and the healthy size and shape, of the affected arterioles.

The topical compositions of the present invention have one or more active compounds described by the following general structure:



wherein:

Z is selected from the group consisting of sulfur, oxygen, and nitrogen;

R_1, R_2, R_3, and R_4 are independently selected from the group consisting of hydrogen, amino, alkyl, alkoxy, alkenyl, alkynyl, hydroxy, aryl, benzyl, phenethyl, thienyl, pyrrolyl, phenyl group, cyclic (saturated or unsaturated), and hydroxyalkyl groups. R_1 through R_4 may represent one or more ring structures, either independently or in combination; and

X is an anion or anionic compound.

When Z is oxygen, sulfur, or nitrogen, the above formula yields oxazolium, thiazolium, or imidozolium compounds, respectively.

A composition according to the present invention may contain one or more of the above described active compounds in any amount up to about 90% of the total weight of the composition (wt.%), preferably up to about 50 wt.%, and, more preferably, up to about 20 wt.% in a physiologically acceptable vehicle.

The active compounds used in the compositions of the present invention may be prepared according to any method. For example, thiazolium compounds for use in the present invention may be prepared according to the procedures described in U.S. Patent No. 5,656,261, which is incorporated herein by reference.

According to the present invention, the active compounds are topically applied in a carrier. As used herein, a carrier is a formulation within which a particular active compound, such as a thiazolium compound, is applied to the skin. The carrier may be a physiologically acceptable carrier that does not produce significant irritation upon contact with human skin. A carrier for use in the present invention can be of any form, such as a solid, a fluid, an emulsion or an aerosol. Examples of a solid carrier include patches, tapes, powders, and other dry solid carrier obvious to

those skilled in the art. Examples of a fluid carrier include creams, lotions, gels, and any other fluid carrier obvious to those skilled in the art.

In addition to above described active compounds, the compositions of the present invention may also contain one or more additional compounds. For example and without limitation, a composition according to the present invention may contain one or more emollients (preferably in an amount up to about 30 wt.%), one or more emulsifiers (preferably in an amount up to about 20 wt.%), one or more preservatives (preferably in an amount up to about 5 wt.%), one or more alcohols (preferably in an amount up to about 95 wt.%), one or more fragrances (preferably in an amount up to about 5 wt.%), one or more thickening agents (preferably in an amount up to about 10 wt.%), one or more humectants (preferably in an amount up to about 25 wt.%), one or more colorants (preferably in an amount up to about 1 wt.%), one or more silicones (preferably in an amount up to about 50 wt.%), one or more exfoliating agents (preferably in an amount up to about 70 wt.%), one or more keratolytic agents (preferably in an amount up to about 50 wt.%), one or more retinoids (preferably in an amount up to about 10 wt.%), one or more sunscreens, such as avobenzene, octyl salicylate, octyl methoxycinnamate, and octocrylene (preferably in an amount up to about 30 wt.%), one or more skin penetration enhancers (preferably in an amount up to about 25 wt.%), one or more anti-inflammatory agents (preferably in an amount up to about 50 wt.%), one or more vitamins (preferably in an amount up to about 50 wt.%), one or more thrombolytic agents (preferably in an amount up to about 50 wt.%), one or more anticlotting agents (preferably in an amount up to about 30 wt.%), one or more capillary protectants (preferably in an amount up to about 70 wt.%), and one or more antioxidants (preferably in an amount up to about 80 wt.%).

Furthermore, other compounds that may be incorporated into the composition include: one or more hormones (preferably in an amount up to about 5 wt.%), one or more antibacterial agents (preferably in an amount up to

about 20 wt.%), one or more analgesics (preferably in an amount up to about 50 wt.%), one or more lipophilic compounds (preferably in an amount up to about 90 wt.%), one or more antihistamine agents (preferably in an amount up to about 20 wt.%), one or more insect repellants (preferably in an amount up to about 90 wt.%), one or more skin cooling compounds (preferably in an amount up to about 90 wt.%), one or more lubricants (preferably in an amount up to about 90 wt.%), one or more anti-fungal agents (preferably in an amount up to about 50 wt.%), one or more skin-whitening agents (preferably in an amount up to about 50 wt.%), and mixtures thereof.

The following are examples of compositions according to the present invention.

Example 1: Oil-In-Water Emulsion Composition

Ingredient	wt.%
3-(2-methyl-2-oxoethyl)-thiazolium chloride	1.00
Glyceryl stearate	8.00
Cetearyl alcohol	1.50
Cetearyl Octanoate	1.50
Octylpalmitate	4.00
Butylene Glycol	5.00
Glycerine	4.00
Methyl Paraben	0.40
Fragrance	0.01
Water	*qs*

Example 2: Cream Composition

Ingredient	wt.%
Cetyl alcohol	2.00
Glyceryl monostearate	2.50
3-propargyl-4-methyl-thiazolium bromide	0.50
White Petrolatum	5.00
3,4-dimethyl-5-(2-hydroxyethyl)-thiazolium iodide	5.00

Octyl Palmitate	8.00
Steareth-2	1.00
Peg-40 Stearate	2.00
Triethanolamine	to pH=6.00
Water	*qs*

Example 3: Lotion Composition

Ingredient	wt.%
Xanthan Gum	0.25
Hydroxyethyl cellulose	0.35
3-ethyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride	2.00
Propylene glycol	5.00
Tocopherol	0.10
Caprylic/Capric triglyceride	9.00
Steareth 2	1.50
Lactic acid	2.00
Ammonium hydroxide	to pH 3.8
Water	*qs*

Example 4: Toner

Ingredient	wt.%
Ethyl alcohol	40.00
2-(2-phenyl-2-oxoethyl)-4-methylthiaxolium bromide	10.00
Glycerine	5.00
Disodium EDTA	0.25
Lactic acid	1.00
Salicylic acid	1.50
Ammonium hydroxide	to pH 4.0
Water	*qs*

Example 5: Ointment

Ingredient	wt.%
Petrolatum	68.99

Shae butter	10.00
Lipophilic rosemary extract	0.01
Apigenin	1.00
3-(2-methoxy-2-oxoethyl) benzothiazolium chloride	20.00

Example 6: Anhydrous Tonic

Ingredient	wt.%
Silicone oil	30.00
Propylene glycol	2.00
Phenethyl isothiocyanate	0.01
3-(2-phenyl-2-oxoethyl)thiazolium chloride	0.5
Fragrance	0.15
Colorant	0.01
Anhydrous ethanol	*qs*

Example 7: Silicone Emulsion

Ingredient	wt.%
Cyclomethicone/Dimethicone copolyol	10.00
Cyclomethicone pentamer	15.00
Sodium Chloride	0.50
Glycerine	5.00
Preservative	0.15
Decylisothiocyanate	1.00
3-(2-phenyl-2-oxoethyl)-4-methylthiazolium chloride	5.00
water	*qs*

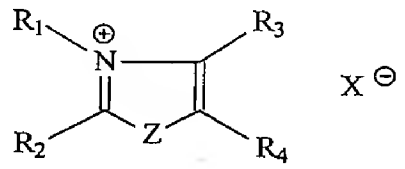
In use, a composition according to the present invention may be applied topically in any amount and according to any schedule. Use of the composition is limited only by the particular circumstances of use, which may include treatment of, for example, skin pigmentation, age spots, wrinkles, lack of elasticity of the skin, poor skin texture, poor skin tone, and poor skin clarity. The particular circumstances of use may also include one or more of the aesthetic goals, such as, reducing dermatological aging

(particularly dermatological aging due to hormonal aging), decreasing skin fragility, preventing and reversing loss of collagen, preventing skin atrophy, promoting/accelerating cell turnover, improving skin firmness/plumpness, improving skin texture, decreasing fine lines and wrinkles, improving skin tone, enhancing skin thickness, decreasing pore size, minimizing skin discoloration, restoring skin luster, minimizing signs of fatigue, reducing acne, and improving skin clarity.

The present invention having been described with particular reference to the preferred forms thereof, it will be obvious that various changes and modifications may be made herein without departing from the spirit and scope of the invention as defined in the appended claims.

Wherefore w claim:

1. A method for the treatment of telangiectasia comprising the step of topically applying to said telangiectasia a composition including one or more active compounds described by the following general structure:



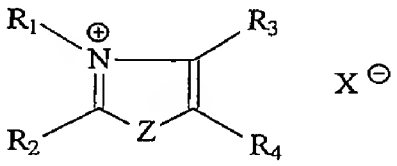
wherein:

Z is selected from the group consisting of sulfur, oxygen, and nitrogen;

R_1, R_2, R_3, and R_4 are independently selected from the group consisting of hydrogen, amino, alkyl, alkoxy, alkenyl, alkynyl, hydroxy, aryl, benzyl, phenethyl, thienyl, pyrrolyl, phenyl group, cyclic, and hydroxyalkyl groups. R_1 through R_4 may represent one or more ring structures, either independently or in combination; and

X is anionic.

2. A method for the treatment of the skin comprising the step of topically applying to said skin a composition including one or more active compounds described by the following general structure:



wherein:

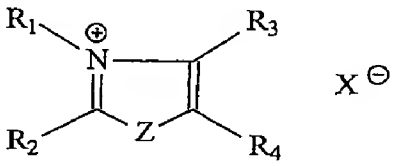
Z is selected from the group consisting of sulfur, oxygen, and nitrogen;

R_1, R_2, R_3, and R_4 are independently selected from the group consisting of hydrogen, amino, alkyl, alkoxy, alkenyl, alkynyl, hydroxy, aryl, benzyl, phenethyl, thienyl, pyrrolyl, phenyl group, cyclic, and hydroxyalkyl groups. R_1 through R_4 may represent one or more ring structures, either independently or in combination; and

X is anionic.

3. The method of claim 2, wherein said treatment is for one or more of the conditions selected from the group consisting of: skin pigmentation, age spots, wrinkles, lack of elasticity of the skin, poor skin texture, poor skin tone, poor skin clarity.

4. A method for improving the aesthetic appearance of the skin comprising the step of topically applying to said skin a composition including one or more active compounds described by the following general structure:



wherein:

Z is selected from the group consisting of sulfur, oxygen, and nitrogen;

R_1, R_2, R_3, and R_4 are independently selected from the group consisting of hydrogen, amino, alkyl, alkoxy, alkenyl, alkynyl, hydroxy, aryl, benzyl, phenethyl, thienyl, pyrrolyl, phenyl group, cyclic, and hydroxyalkyl groups. R_1 through R_4 may represent one or more ring structures, either independently or in combination; and

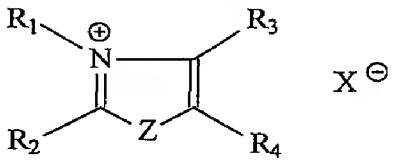
X is anionic.

5. The method of claim 4, wherein the improvement in aesthetic appearance includes at least one of the following:

a. Reducing dermatological aging, particularly dermatological aging due to hormonal aging;
b. Decreasing skin fragility;
c. Preventing and reversing loss of collagen;
d. Preventing skin atrophy;
e. Promoting/accelerating cell turnover;

f. Improving skin firmness/plumpness;
g. Improving skin texture;
h. Decreasing fine lines and wrinkles;
i. Improving skin tone;
j. Enhancing skin thickness;
k. Decreasing pore size;
l. Minimizing skin discoloration;
m. Restoring skin luster;
n. Minimizing signs of fatigue;
o. Reducing acne; and
p. Improving skin clarity.

6. A composition for topical application to telangiectasia, said composition comprising a physiologically acceptable carrier and one or more active compounds described by the following general structure:



wherein:

Z is selected from the group consisting of sulfur, oxygen, and nitrogen;

R_1, R_2, R_3, and R_4 are independently selected from the group consisting of hydrogen, amino, alkyl, alkoxy, alkenyl, alkynyl, hydroxy, aryl, benzyl, phenethyl, thienyl, pyrrolyl, phenyl group, cyclic, and hydroxyalkyl groups. R_1 through R_4 may represent one or more ring structures, either independently or in combination; and

X is anionic.

7. The composition of claim 6, wherein said one or more active compounds are selected from the group consisting of: 3-(2-methyl-2-oxoethyl)-thiazolium chloride, 3-propargyl-4-methyl-thiazolium bromide, 3,4-dimethyl-5-(2-hydroxyethyl)-thiazolium iodide, 3-ethyl-5-(2-

hydroxyethyl)-4-methylthiazolium chloride, 2-(2-phenyl-2-oxoethyl)-4-methylthiaxolium bromide, 3-(2-methoxy-2-oxoethyl) benzothiazolium chloride, 3-(2-phenyl-2-oxoethyl)thiazolium chloride, 3-(2-phenyl-2-oxoethyl)-4-methylthiazolium chloride, and mixtures thereof.

8. The composition of claim 6, wherein said physiologically acceptable carrier may be applied to skin without irritation and is selected from the group consisting of comprises a solid, a fluid, an emulsion, an aerosol, and mixtures thereof.

9. The composition of claim 8, wherein said physiologically acceptable carrier is selected from the group consisting of: patches, tapes, powders, a dry solid, creams, lotions, gels, and combinations thereof.

10. The composition of claim 6, further comprising one or more additional compounds selected from the group consisting of: emollients, emulsifiers, preservatives, alcohols, fragrances, thickening agents, humectants, colorants, silicones, exfoliating agents, keratolytic agents, retinoids, sunscreens, skin penetration enhancers, anti-inflammatory agents other than thiazolium compounds, vitamins, thrombolytic agents, anticlotting agents, capillary protectants, antioxidants, hormones, antibacterial agents, analgesics, lipophilic compounds, antihistamine agents, insect repellants, skin cooling compounds, lubricants, anti-fungals, and mixtures thereof.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US01/04304

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) :A61K 31/415, 31/42, 31/425
US CL :514/365, 374, 369
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/365, 374, 369

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS-ON-LINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,268,176 A (ZNAIDEN et al.) 07 December 1993, see the entire document.	1-10

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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